Essential hypertension: a sign in search of a disease

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The concept of disease is of cardinal importance in medical practice. The current definition has developed over more than 200 years. It includes a distinctive natural history and identifiable cellular changes. Pickering proposed a fundamental alteration to the definition when he suggested that essential hypertension is a quantitative disease without causative cellular change distinguishing normal from abnormal. The nature of essential hypertension has been confused from the beginning because of a category error. Injury is conceptually distinguished from disease. Essential hypertension, defined as elevated blood pressure together with its cardiovascular consequences, is found to be neither an injury nor a disease according to current definitions. Instead, essential hypertension refers to a treatment group just as "the fevers" did in an earlier century. One effect on patients of the failure to resolve this diagnostic paradox is the burden of suffering from the label of "disease" rather than from a state that may be substantially due to their own behaviour. A theoretical consequence of importance for psychiatric theory is that the disease status of functional disorders can no longer be defended by an appeal to the existence of a quantitative disease of blood pressure.

Le concept de la maladie est d'une importance cruciale dans la pratique de la médecine. La définition actuelle a évolué sur plus de 200 ans. Elle comprend une histoire naturelle distincte et des changements cellulaires identifiables. Pickering a proposé une modification fondamentale de la définition en laissant entendre que l'hypertension artérielle essentielle était une maladie quantitative sans modification cellulaire causale permettant de distinguer un état normal d'un état anormal. La nature de l'hypertension artérielle essentielle suscite la confusion depuis toujours à cause d'une erreur de catégorie. On établit une distinction conceptuelle entre blessure et maladie. Définie comme une pression artérielle élevée accompagnée de répercussions cardio-vasculaires, l'hypertension artérielle essentielle n'est ni une blessure ni une maladie, selon les définitions en vigueur. L'expression désigne plutôt un groupe thérapeutique comme «la fièvre» en désignait un par le passé. Comme on n'a pas tranché ce paradoxe diagnostique, il en résulte notamment que les patients souffrent d'une «maladie» plutôt que d'un état qui peut être en grande partie lié à leur propre comportement. Il en résulte une conséquence théorique importante en psychiatrie théorique : on ne peut plus défendre l'état morbide de troubles fonctionnels en se basant sur l'existence d'une maladie quantitative de la pression sanguine.

Disease is the cardinal concept of medicine. It is to scientific medicine what mass is to physics, molecule to chemistry and cell to biology. The two most far-reaching conceptual advances in medicine since Hippocrates have concerned its definition. For 1700 years after Hippocrates the term disease signified a lack of ease — there was dis-ease in the sense of people suffering but no clear-cut concept of individual diseases. Restrictions in the sense during the 17th and 19th centuries

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sharpened the definition and brought specific diseases into focus. The emergence of an operational definition of the basic unit in medical theory then led to unprecedented advances, as had happened in physics, chemistry and biology.

The first restriction occurred in 1676 when Sydenham[1] proposed an ontologic theory of disease. He suggested that qualitatively separate diseases exist and are revealed in patients by a characteristic progression of symptoms and signs: This definition provided the basis for modern clinical medicine by allowing reliable diagnosis of a specific disease from a record of its natural history.

The second restriction occurred in 1858 when Virchow[2] stated that all disease processes were located in cells. Before then physicians had located these processes at higher levels of bodily organization: Hippocrates suggested that they occurred in the body as a whole, Morgagni in organs and Bichat in tissues.[3] Virchow's insight into the cellular basis of disease succeeded where earlier descriptions had failed; many diseases were clarified relatively quickly after publication of his book on cellular pathology. Our failure to clarify the enigma of hypertension is a monument to our persistent failure to implement his insight correctly.

In 1956 Pickering[4] proposed a third fundamental change in the definition of disease. His demonstration of the unimodal distribution of blood pressure in the general population confronted physicians with a diagnostic paradox by establishing that normotensive and hypertensive people blend together indistinguishably. Essential hypertension, therefore, differs radically from established physical disease by not having a qualitative criterion that allows a definitive diagnosis.

For the first time the underlying paradigm of scientific medicine seemed to have been violated. Patients did not differ qualitatively from nonpatients except through physicians' arbitrary agreement on a dividing line. Pickering[4] resolved this by giving essential hypertension a unique status. He proposed that it be considered a type of disease "not hitherto recognized in medicine in which the defect is one of degree not of kind, quantitative not qualitative." This is the medical equivalent of changing the definition of mass, molecule or cell. It extends the term disease to include continuously distributed states, such as high blood pressure, for which there is no pathological diagnosis. Establishment of such a state constitutes a diagnosis by exclusion in that it requires the absence of a cellular fault: "[There is no] single histological or pathological entity characteristic of the disease essential hypertension."[4]

To propose a new definition is to propose a new theory.[5,6] However, Pickering's quantitative concept of disease was not new; it returned to the meaning that had prevailed before 1858. Although the unimodal distribution of blood pressure has been accepted the notion of quantitative disease has not been, but neither has it been rejected. Indeed, there is no accepted formulation of raised pressure without evident cause.

If these issues cannot be clarified by an appeal to the definition of disease used for the past 130 years, then the theoretic foundation of medicine is seriously flawed. We examined the diagnostic paradox of essential hypertension in terms of the method of diagnosing disease used by physicians in medical (but not psychiatric) practice. We then formulated essential hypertension without Pickering's fundamental change in the definition of disease.

Essential hypertension

The term hypertension is used ambiguously in medical literature. Dictionaries define it as raised arterial pressure,[7-12] but textbooks refer to it as a complex disease.[13,14] These meanings merge in discussion of early essential hypertension characterized only by raised pressure. Some writers define elevated pressure and hypertension differently but use them interchangeably. Others define essential hypertension as high blood pressure without evident cause together with its cardiovascular consequences but diagnose it when faced with only unexplained raised pressure.

Two forms of hypertension are recognized, secondary or symptomatic and essential. Symptomatic hypertension results from several conditions that increase pressure but are otherwise unrelated. There is no confusion about its nature — it is a sign, not a disease.

Essential hypertension refers to persistently raised arterial pressure without evident cause together with any consequent cardiovascular lesions. The nature of this form of hypertension has remained elusive since it was first described in 1877.[15]

Origin of the confusion

"Hypertension is the leading cause of death and disability among adults. . . . It remains the major risk factor for coronary, cerebral and renal vascular diseases, the causes of more than half of all deaths in the United States."[16] Despite such prominence, views of the nature of essential hypertension have led to descriptions of it as a sign,[4,17] a myth,[18] a genetic disease,[19,20] a disease of regulation,[21,22] a multifactorial disease,[22] a completely new, nonvirchowian disease of quantity,[4] an endocrine disease,[23] a psychosomatic disorder,[24] a syndrome[25] and accelerated aging.[4] It has been suggested that malignant hypertension is a disease but that less severe hyper-

tension is not.[26] Pickering[27] listed six additional names for essential hypertension used between 1877 and 1911, none of which are current. Although investigated more than any other disease[28] essential hypertension has been in conceptual disarray from the start.

Given this long-standing confusion, should essential hypertension be classified as a disease? We will answer this question, with explicit reference to the current definition of disease, by examining its natural history using Sydenham's clinical identification and its pathological basis using Virchow's cell doctrine.

The first clinical indication of essential hypertension is an exaggeration in supplemental pressure (casual minus basal), which, it has been said, may be psychologically caused.[4] There can be disagreement about whether pressure is raised depending on which arbitrary cut-off point is chosen to indicate onset of the disease, whether the fourth or the fifth heart sound marks diastolic pressure and whether one reading is taken or several are averaged. The pressure is often labile. Thus the onset of raised pressure does not have a definite indicator. Pickering stated that "a great deal of time and energy has been wasted in trying to define the onset . . . of the disease"[27] and that "because of its nature . . . it is not possible to say when the disease begins."[29]

After the diagnosis, the pressure remains labile in some patients and continues to increase in others. It may reach a plateau, sometimes having minimal ill effects.[4,30] In most patients the pressure remains mildly elevated, and in some it returns to normal levels without treatment[4] or with changes in lifestyle.[26,31-37] In 2% of cases the pressure rises rapidly, causing papilledema and death if not treated promptly. In 1915, when this variability was unclear, Allbutt[38] suggested that essential hypertension "is a malady in which at or towards middle life, blood pressure rises excessively, a malady having a course of its own and deserving the name of 'disease'." He used Sydenham's formulation to diagnose a disease of pressure on the basis of a characteristic clinical course. Although currently considered to be a disease, unexplained high blood pressure does not have a characteristic natural history; on the contrary, it exhibits almost every conceivable course.

The definition of essential hypertension conflicts with Virchow's cell doctrine. Consider two observations. First, in 1914 Fisher,[39] an insurance company executive, reported a significant association between blood pressure and risk of death on the basis of an actuarial study of 19 339 people. He showed that an increase in the death rate was associated with a persistent increase in the mean group systolic pressure of 15 mm Hg above the average for age; he suggested that systolic pressures exceeding this in individuals be considered pathologic. His recommendation that a significant association concerning insurability be used in place of Virchow's cellular fault is now widely accepted. Unfortunately, it confuses cause with noncause:[40] insurance premiums can be apportioned among people according to group risk, but diagnosis of disease cannot. For the half century before 1914 it had been necessary to demonstrate a pathological finding in order to diagnose a disease; this is still true for all diseases except essential hypertension, for which Virchow's cellular disease process has been replaced by an actuarial risk.

The second observation concerns the division of hypertension into two forms. It was thought initially that all cases of essential hypertension might prove to be symptomatic. Platt[41] was perhaps the last to champion that view in the Platt–Pickering debate when he tried unsuccessfully to establish a genetically determined bimodal distribution of pressure around a disjunction at 150/90 mm Hg. No one has found a specific cause for essential hypertension; furthermore, it is now defined by the absence of a causative disease process. Virchow's definition of disease is the precise opposite — the presence of a cellular disease process.

Essential hypertension, then, does not have the necessary characteristics of a disease. But it continues to be so diagnosed. Why is this?

Underlying logical fallacy

Pickering's epidemiologic finding revealed that a category error had been made in taking essential hypertension to be a disease. Consider these two statements: "Pneumonia is a disease of the lung" and "Pneumonia is a disease of the brain." Both have meaning and are grammatically correct; the first is true, the second false. Now consider "pneumonia is purple." Although grammatically correct it is neither true nor false; it is absurd. It is a category error, a logical entity first described by Ryle,[42] in 1937. He asserted that subjects (of propositions) of different logical types collect different sets of predicates. In the example given, pneumonia may have disease as a possible predicate but not purple. The use of a predicate with a subject of the wrong logical type results in a category error and asserts a meaningless proposition. The incorporation of such absurd propositions into scientific theory entails logical contradictions called antinomies.

Diseases arise from pathological processes in cells, but signs are injuries to tissues caused by underlying cellular disease processes. Diseases and signs are therefore of different logical types and collect different sets of predicates. Hence, to classify a sign or a group of conditions showing a common

sign as a disease is to commit a category error. One consequence of such an error will be the emergence of antinomies such as Pickering's epidemiologic finding. The discovery of a disease indistinguishable from normality is the kind of absurdity a category error may generate. Furthermore, once this conceptual error was made in the case of hypertension extensive experimental investigation could not and did not resolve the resulting confusion.

If essential hypertension should not be classified as a disease how should it be conceptualized? We began by noting that the concept of disease is central to medical theory. In practice medicine is occupied as much with injury as it is with disease, and these will now be distinguished as a first step in formulating essential hypertension.

Injury versus disease

Unlike disease the medical definition of injury has not been refined, because trauma has remained underresearched and is conceptually impoverished.[43] Nevertheless, injury has a practical meaning in medicine: "damage inflicted to the body usually by an external force,"[10] or, more fully, a disruption of the integrity of a tissue or an organ by external forces that are usually mechanical but can also be chemical, electrical, thermal or radiant.

Injury and disease have little in common. They are distinguished by at least four features, two of which arise from the definition of injury. First, injury refers to the impact of a force, not to a living disease process, and, second, it involves damage primarily at the higher level of tissues and organs, not at the cellular level.

The third distinction lies in the nature of the cause–effect relation. Consider exposing a living body to radiant energy. The initial damage is a burn. As with all injuries the dose–response and dose–effect relations are graded and quantitative and have clinical thresholds.[44] The damage is not self-propagating and is followed by healing. The other consequence of this exposure is a disease process: increased frequency of genetic mutation (response) and consequent neoplasia (effect). Here, there is no dose–effect relation; a cancer is not worse for having been induced by more radiation. The dose–response relation is graded, with no known lower clinical threshold.[44] This process is stochastic and characterizes the induction of a disease process that begins randomly in a single cell and then grows autonomously.

Fourth, injury and disease differ histologically, as Hunter[45] implied in 1794: "There is a circumstance attending accidental injury which does not belong to disease, namely, that the injury done, has in all cases a tendency to produce both the disposition and the means of cure." In modern terms cellular changes at a site of injury are the tissue damage itself or a normal reparative response. In disease there is a pathological cellular process that does not tend to cure; on the contrary, it is destructive.

The effects of pressure

Keeping in mind these four distinctions between injury and disease, consider pressure and its consequences. The left ventricle and the arterial tree down to the high-resistance vessels form a functional compartment of continuously varying size. It is unusual in that it houses a pulsatile flow of viscous liquid under high pressure from before birth until death. Its walls are unique among the tissues of the body in being exposed to large pulse pressures fluctuating around a high mean pressure. At some sites the walls are also subjected to intermittent shearing forces related to turbulent flow. The transmural pressure averages 100 mm Hg, several orders of magnitude greater than in other compartments. For example, venous pressure varies from 0 to 10 mm Hg, right atrial pressure from 0 to 20 mm Hg and lymphatic pressure from 1 to 2 cm H_2O. Furthermore, except for the right atrium, compartmental pressures are steady and cause stresses that are trivial compared with those acting on arterial walls. Wall tension is 10 to 30 dyn/cm in capillaries and venules and 20 000 dyn/cm in the vena cava. In the ascending aorta pressure fluctuates around a mean of 200 000 dyn/cm more than once per second throughout life. It is not surprising that the effects of raised pressure can become a clinical problem.

These hemodynamic facts do not result from a fault of design. Servicing the metabolic needs of a vast number of cells dispersed in space requires a source of pressure in large, elastic conduit vessels proximal to separately variable sets of small, high-resistance vessels. If this pressure rises excessively vessel walls may rupture or the heart may fail. The high tension in arterial walls is borne primarily by nonliving, intercellular fibres of collagen and elastin. The burden falling on these fibres becomes more marked at pressure peaks and is magnified by increasing mean pressure. The purely physical phenomena of fatigue due to chronic stress and rupture due to acute maximal stress may therefore be expected with increasing pressure.[46,47]

Three age-related changes that occur in arteries augment the problem.[48] The diameter of the lumen increases with age, and since wall tension is directly proportional to the vessel radius this increased cross-sectional area alone will increase vessel wall fatigue. In addition, arteries lengthen and become tortuous; the consequent turbulent flow augments fatigue by shifting more energy from the flowing

blood to the adjacent wall. Finally, the nonliving components of the arterial walls stiffen with age, increasing pulse pressure and consequently the rate of change of pressure with time; like the turbulent flow from lengthened and tortuous arteries the increased pulse pressure transfers more energy from the flowing blood to the adjacent wall.

Essential hypertension re-evaluated

The definition of essential hypertension must take into account the characteristics of the relation between pressure and its effects. Those characteristics can now be examined in light of the four distinctions between injury and disease.

First, whatever the consequences of increased pressure they are caused by a simple force. Evidence that they are derived from raised pressure and no other bodily process is provided by unilateral renal disease, coarctation of the aorta and pulmonary hypertension. Damage to arterial walls in all cases is directly proportional to the pressure alone.[49] Second, raised pressure causes damage to tissues and organs, not to cells. We speak of a cancerous cell but not of a hypertensive cell. Third, dose (pressure exerted over time) is quantitatively related both to response (the amount of damaged tissue) and to effect.[50] This relation holds for the whole range of pressures. There are not two kinds of blood pressure, injurious and noninjurious; isolated systolic hypertension is as dangerous as elevated diastolic pressure.[51] The effects can be acute or chronic. The frequency of the acute complications (fibrinoid necrosis of arterioles, renal failure and left ventricular failure) is directly related to the pressure, and the complications are relieved by reduction of the pressure.[17] The frequency of the chronic complications (arteriosclerosis, medial necrosis and aneurysm) is also directly related to the magnitude and duration of raised pressure.[17] These complications occur throughout the population, increase in frequency as pressure rises and decrease as it falls. Last, damage and reparative responses are found in the vascular tissues but are not a cellular disease process caused by raised pressure. Raised pressure would not be a disease even if such a process were found, just as radiation is not a disease even though it can cause a neoplasm.

It is clear, then, that the relation between high blood pressure and the resulting cardiovascular lesions is an example of the relation between a simple force and the injuries it either causes or aggravates.[17,46] This relation is graded and quantitative, regardless of what increases the pressure. Essential and symptomatic hypertension are the same in this regard.[29] Pickering[52] interpreted this finding — but only in the case of essential hypertension — as primary evidence for the existence of quantitative disease: "The quantitative relationship between arterial pressure and its consequences is the chief evidence for the hypothesis that essential hypertension represents a kind of disease hitherto unrecognized by medicine, a disease in which the deviation from the norm is one of degree, not of kind, a quantitative rather than a qualitative disease." It is contradictory to assert that pressure raised by known conditions is a sign and by unknown conditions (with its consequences) a disease. In both cases elevated pressure damages vascular tissue, and — as with all forces — the damage is quantitative: more force, more injury.

This view of essential hypertension has remained elusive for two reasons. First, once a category error is made and acquires the force of dogma, only its explication will clear resulting confusion. The error in this case has remained hidden. Second, the injury is a singular one. Virtually all other injuries are caused by an external force of known origin; in essential hypertension vascular injury results from an unexplained increase in an internal force. Most forces affect few people, but this internal force is ubiquitous. All of us are born with a certain level of blood pressure that may rise slowly over the decades. The rise can become mechanically self-perpetuated[53] and sometimes irreversible. In such a way this unusual injury mimics the course of a self-propagated disease.

Once essential hypertension is viewed as idiopathically raised pressure causing vascular injury, we can understand why it has proved so difficult to classify as a disease and why such a classification is erroneous. The two forms of hypertension constitute a prescientific taxonomy of increased pressure: symptomatic hypertension groups diverse conditions solely because they cause raised pressure, whereas essential hypertension groups diverse vascular injuries solely because they are caused by unexplained elevated pressure. The term essential hypertension does not categorize people according to the same kind of scientific medical principle that underlies the term pneumonia. It does not signify what it is generally accepted to signify: a disease entity that has a recognized natural history and is caused by a characteristic pathological cellular process, as determined by laboratory findings. Furthermore, it does not refer to an injury; raised pressure is not damage to tissues and organs.

In cases of symptomatic hypertension the elevated pressure is a simple sign; together with its consequences it is a complex sign of the disease that is causing the raised pressure. In cases of essential hypertension, on the other hand, the situation is fundamentally different. Although the elevated pressure and its consequences are not physically distinct from those in symptomatic hypertension they cannot

be taken as a complex sign of an underlying disease process, because by definition there is no such process. The raised pressure and its consequences constitute essential hypertension itself. This statement will remain true whatever the outcome of current work on the possibility of a pressor allele. If some people are found to possess the allele they would then become classified as having secondary hypertension; those lacking the allele would still be classified as having essential hypertension.

Essential hypertension is, however, a useful clinical classification. Patients with unexplained increased pressure will suffer known consequences that can be averted by treatment. Both the consequences and the treatment are independent of the unknown cause of the raised pressure; that is, the treatment remains empiric at present. In this sense, these patients form a coherent treatment group just as did those patients with "the fevers" in earlier centuries. Essential hypertension will remain useful as a clinical category as long as the presumably varied causes of elevated pressure remain unknown.

The suggestion that this issue of classification is merely semantic arises from the idea that definitions are nominal,[54] an agreement on how to use terms. However, the definition of disease is not only nominal but also existential, and our choice will have real effects. Two consequences of the way we resolve the paradox of essential hypertension reveal that this is more than a semantic issue.

First, there is evidence that labelling people as having the "disease" essential hypertension (the silent killer) is harmful.[55,56] There is no evidence that telling patients they are injuring themselves and can stop doing so has a similar detrimental effect. Drug treatments create many personal problems that may go unnoticed by the prescribing physician.[57] Patients suffering from uncomplicated mild to moderate essential hypertension can be told that many behavioural changes may result in a lowering of their blood pressure. Loss of weight in the obese, reduced sodium intake, reduced alcohol consumption and mild exercise by inactive people can all be advocated.[58-63] Different measures are effective in different people and can yield a decrease in blood pressure of 10 to 15 mm Hg. This decrease would not help all patients with established increases in pressure, but it would affect those with reversible changes. It would also cause a decline in the number of new cases and thus a diminished prevalence. A decrease of only 10 mm Hg in the mean pressure of the population would shift the entire distribution to the left and would have an important effect on morbidity and mortality rates.

It is not yet clear why these behavioural changes lower blood pressure in some people and not in others. Nevertheless, we can make these recommendations without a full knowledge of the underlying mechanisms, as we did in the case of smoking and the provision of sewage disposal services; in neither of these two instances did we wait until complete scientific proof was available.

Furthermore, if we are no longer preoccupied with the cause of the "disease" we might begin to ask questions about why blood pressure does not rise excessively in some people at or nearing middle life. Are they of lower weight? Do they drink less alcohol? Do they consume less salt? Are they active? The answers to these questions are unknown.

A second consequence of accepting essential hypertension as a disease is that the same idea can be used to prevent resolution of other difficulties in medical theory. Consider the century-old controversy over the status of "psychogenic diseases." They are defined in terms of an absence of a cellular fault, and they are diagnoses of exclusion. They would therefore qualify as quantitative diseases. Not one of them has a pathological diagnosis. Lack of evidence of a biomedical disease does not prove its absence, but that lack should not be used to invent a new kind of disease. Confusion about the nature of psychiatric disorders arose for the same reasons as it did about the nature of essential hypertension, and it persists because the category error remains largely hidden.

One argument against classifying the functional states treated by psychiatrists as diseases is that they have no pathological diagnosis; they blend imperceptibly into normality. Psychiatric theorists have countered with the argument that because there is at least one physical disease that cannot be qualitatively diagnosed (essential hypertension) the disease status of the functional conditions they treat cannot be challenged on this ground.[64-66] This obfuscation by psychiatrists blurs the distinction between personal conduct, which one is responsible for, and impersonal disease processes, which befall one. Perhaps this issue alone justifies clearing the confusion surrounding the clinical consequences of high blood pressure without evident cause.

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